Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

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Summary

Background Acute acidaemia is frequently observed during critical illness. Sodium bicarbonate infusion for the treatment of severe metabolic acidaemia is a possible treatment option but remains controversial, as no studies to date have examined its effect on clinical outcomes. Therefore, we aimed to evaluate whether sodium bicarbonate infusion would improve these outcomes in critically ill patients.

Methods We did a multicentre, open-label, randomised controlled, phase 3 trial. Local investigators screened eligible patients from 26 intensive care units (ICUs) in France. We included adult patients (aged ≥18 years) who were admitted within 48 h to the ICU with severe acidaemia (pH ≤7·20, $PaCO_2$ ≤45 mm Hg, and sodium bicarbonate concentration ≤20 mmol/L) and with a total Sequential Organ Failure Assessment score of 4 or more or an arterial lactate concentration of 2 mmol/L or more. We randomly assigned patients (1:1), by stratified randomisation with minimisation via a restricted web platform, to receive either no sodium bicarbonate (control group) or 4·2% of intravenous sodium bicarbonate infusion (bicarbonate group) to maintain the arterial pH above 7·30. Our protocol recommended that the volume of each infusion should be within the range of 125–250 mL in 30 min, with a maximum of 1000 mL within 24 h after inclusion. Randomisation criteria were stratified among three prespecified strata: age, sepsis status, and the Acute Kidney Injury Network (AKIN) score. The primary outcome was a composite of death from any cause by day 28 and the presence of at least one organ failure at day 7. All analyses were done on data from the intention-to-treat population, which included all patients who underwent randomisation. This study is registered with ClinicalTrials.gov, number NCT02476253.

Findings Between May 5, 2015, and May 7, 2017, we enrolled 389 patients into the intention-to-treat analysis in the overall population (194 in the control group and 195 in the bicarbonate group). The primary outcome occurred in 138 (71%) of 194 patients in the control group and 128 (66%) of 195 in the bicarbonate group (absolute difference estimate −5·5%, 95% CI −15·2 to 4·2; p=0·24). The Kaplan-Meier method estimate of the probability of survival at day 28 between the control group and bicarbonate group was not significant (46% [95% CI 40–54] *vs* 55% [49–63]; p=0·09. In the prespecified AKIN stratum of patients with a score of 2 or 3, the Kaplan-Meier method estimate of survival by day 28 between the control group and bicarbonate group was significant (37% [95% CI 28–48] *vs* 54% [45–65]; p=0·0283). Metabolic alkalosis, hypernatraemia, and hypocalcaemia were observed more frequently in the bicarbonate group than in the control group, with no life-threatening complications reported.

Interpretation In patients with severe metabolic acidaemia, sodium bicarbonate had no effect on the primary composite outcome. However, sodium bicarbonate decreased the primary composite outcome and day 28 mortality in the a-priori defined stratum of patients with acute kidney injury.

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Introduction

Acute acidaemia is frequently observed during critical illness, with a reported incidence varying from 14% to 42%.[1–5] Persistent acidaemia has been associated with poor prognosis,[1–3,6] with a mortality rate as high as 57% when the pH stays below 7·20.[5] Along with case-specific treatment, improvement of tissue perfusion and supportive measures such as mechanical ventilation and renal-replacement therapy are the cornerstones of severe metabolic acidaemia management in critically ill patients.[2,3,7] Because an acidotic cellular environment can cause cellular dysfunction, intravenous sodium bicarbonate administration to increase the pH might also be beneficial. In a survey done in North America, more than two-thirds of the programme directors in nephrology or intensive care units (ICUs) declared that they used sodium bicarbonate for the treatment of acidaemia with hyperlactataemia.[8]

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed from Jan 1, 1990, to Feb 1, 2018, using the search terms "sodium bicarbonate" or "metabolic acidemia". Studies were included if they evaluated sodium bicarbonate infusion as an intervention to treat severe metabolic acidaemia. Our review indicates that sodium bicarbonate infusion to increase the arterial pH in this condition has been sparsely evaluated. Animal studies, single centre crossover studies with physiological parameters as a main outcome, and reviews from experts have recommended against its use. Surveys and observational studies have, however, reported that more than half of the critical care physicians or nephrologists would consider sodium bicarbonate infusion for a patient with severe metabolic acidaemia whatever its cause. Finally, the 2017 Surviving Sepsis Campaign stated that "the effect of sodium bicarbonate administration on hemodynamics and vasopressor requirements at lower pH (than 7–15 as well as the effect on clinical outcomes at any pH level, is unknown" and that "no studies have examined the effect of bicarbonate administration on outcomes".

Added value of this study

This is the first large randomised clinical trial comparing two groups of no sodium bicarbonate infusion (control group) with sodium bicarbonate infusion (bicarbonate group) in 400 critically ill patients with severe metabolic acidaemia (pH ≤7·20) from 26 Intensive Care Units. In this trial, we report that in the overall population sodium bicarbonate infusion was not associated with an improvement in the primary outcome (ie, composite criteria of organ failure at day 7 and any cause of death at day 28). In the a-priori defined clinical stratum of patients with acute kidney injury (with Acute Kidney Injury Network scores of 2 or 3 at enrolment), the primary outcome occurred less frequently in the bicarbonate group than in the control group. Additionally, the number of days alive and free from renal-replacement therapy was higher in the bicarbonate group than in the control group both in the overall study population and in the a-priori defined stratum of patients with acute kidney injury. No other organ support parameters were different among treatment groups.

Implications of all the available evidence

The findings of the BICAR-ICU trial suggest that sodium bicarbonate infusion is associated with an improved outcome and a reduced rate of mortality from enrolment to day 28 in critically ill patients with severe metabolic acidaemia (pH ≤7·20) and acute kidney injury. Sodium bicarbonate infusion was also associated with more days alive and free from renal-replacement therapy. However, in the overall non-selected patients, sodium bicarbonate infusion was not associated with a clinical outcome. Further studies should be done to investigate whether sodium bicarbonate infusion might improve survival in a larger dataset and in selected patients with severe metabolic acidaemia and acute kidney injury.

Despite the frequency of its use in ICUs across the world, the effect of sodium bicarbonate infusion for the treatment of metabolic acidaemia remains controversial.[9] Small physiological studies,[10,11] along with retrospective or observational studies,[12,13] have not shown clear conclusions. The reluctance to use sodium bicarbonate for the treatment of severe metabolic acidaemia might be related to the absence of cardiovascular effects in two physiological studies[10,11] and potential side-effects, principally intracellular acidification due to the accumulation of carbon dioxide and the risk of hypocalcaemia.[3,10,14] However, sodium bicarbonate could compensate for the deleterious effects of acidotic cells on cardiovascular and oxygen delivery, and might delay or avoid unnecessary early renal-replacement therapy.

The 2016 update of the Surviving Sepsis Campaign International Guidelines for Management of Sepsis and Septic Shock[15] suggested that the effect of sodium bicarbonate administration on haemodynamics and vasopressor requirements at lower pH as well as its effect on clinical outcomes at any pH level is unknown, and no studies have examined the effect of sodium bicarbonate administration on clinical outcomes. The absence of high-level evidence leaves ICU clinicians uncertain whether sodium bicarbonate infusion is beneficial, ineffective, or indeed harmful to patients with severe metabolic acidaemia. Given such uncertainties, we aimed to evaluate whether sodium bicarbonate infusion would improve clinical outcome in critically ill patients with severe metabolic acidaemia. Specifically, we hypothesised that early sodium bicarbonate infusion compared with no infusion would result in fewer deaths from any cause by 28 days and lower incidence of at least one organ failure at 7 days in adult ICU patients with severe metabolic acidaemia.

Methods

Study design and patients

We did a multicentre, open-label, randomised controlled, phase 3 trial. Local investigators screened eligible patients from 26 ICUs in France. The study protocol and statistical analysis plan was approved for all centres by a central ethics committee (Comité de Protection des Personnes Sud-Est IV, Montpellier, France; EudraCT, number 2014-000245-73) in accordance with both French law and the Declaration of Helsinki.

We included adult patients (aged ≥18 years) who were admitted within 48 h to the ICU with severe acidaemia (pH ≤7·20, $PaCO_2$ ≤45 mm Hg, and sodium bicarbonate concentration ≤20 mmol/L)[5] and with a total Sequential Organ Failure Assessment (SOFA) score of 4 or more or an arterial lactate concentration of 2 mmol/L or more.

We excluded patients who met the following main exclusion criteria: respiratory acidosis, proven digestive or urinary tract loss of sodium bicarbonate (volume loss ≥1500 mL per day), stage IV chronic kidney disease,[16] ketoacidosis, and sodium bicarbonate infusion (including renal-replacement therapy) within 24 h before screening. The appendix provides the full exclusion criteria.

We obtained written informed consent from the patient or a relative upon study inclusion. However, considering the severity of the illness, the fact that most of these patients would be unable to consent (sedation or potential delirium)[17–19] and that their proxies might not be contactable at the time of inclusion, a deferred consent process for emergency situations was enabled. When deferred consent was used, written permission to pursue the research was obtained from the patient or proxy as soon as possible. If this consent was not obtained, the patient's data were not used and they were withdrawn from the trial.

Randomisation and masking

We randomly assigned eligible patients within 48 h of ICU admission in a one-to-one ratio to receive either no sodium bicarbonate infusion (control group) or sodium bicarbonate infusion (bicarbonate group). We randomly assigned patients by stratified randomisation with minimisation using a computer-generated allocation sequence accessible from each centre through a secured-dedicated website with stratification according to study site and three prespecified factors: age with a cutoff of 65 years, presence or absence of suspected sepsis,[20,21] and presence or absence of Acute Kidney Injury Network (AKIN) score of 2 or 3. Because sodium bicarbonate infusion influences arterial pH levels and because routine arterial blood gases must be done in critically ill patients, masking of the physicians and nurses was not feasible.

Procedures

In the intervention group, 4·2% sodium bicarbonate was intravenously infused with the aim of achieving an arterial pH of 7·30 or more during the 28-day ICU admission or ICU discharge because preliminary results suggested that arterial pH in survivors approximated 7·30 by day 1 although persistent severe acidaemia was observed in non-survivors.[5] Our protocol recommended that the volume of each sodium bicarbonate infusion should be within the range of 125–250 mL in 30 min, with a maximum of 1000 mL within 24 h after inclusion, and that measurement of arterial blood gas should be done 1–4 h after the end of each infusion (appendix p 17). Hypertonic 4·2% sodium bicarbonate was chosen according to the scarce literature available,[10,11,22] the current practice when sodium bicarbonate is used as reported by Jung and colleagues,[5] and the objective of titrating a pH target of 7·30 or more.

In both groups, indications for renal-replacement therapy were standardised. Upon admission, urgent renal-replacement therapy was strongly recommended in the event of kalaemia that was more than 6·5 mmol/L with electrocardiogram signs or cardiogenic pulmonary oedema with no urine output, or both. At 24 h after inclusion, renal-replacement therapy was recommended when two of three criteria were present: urine output less than 0·3 mL/kg per h for at least 24 h, arterial pH less than 7·20 despite resuscitation, and kalaemia more than 6·5 mmol/L. Each study site chose the method of renal-replacement therapy according to the local guidelines, which provided additional base because the dialysis included sodium bicarbonate as a buffer.[23] In both groups, initiation of invasive mechanical ventilation was indicated if patients had one major or two minor predefined clinical events (appendix).[24]

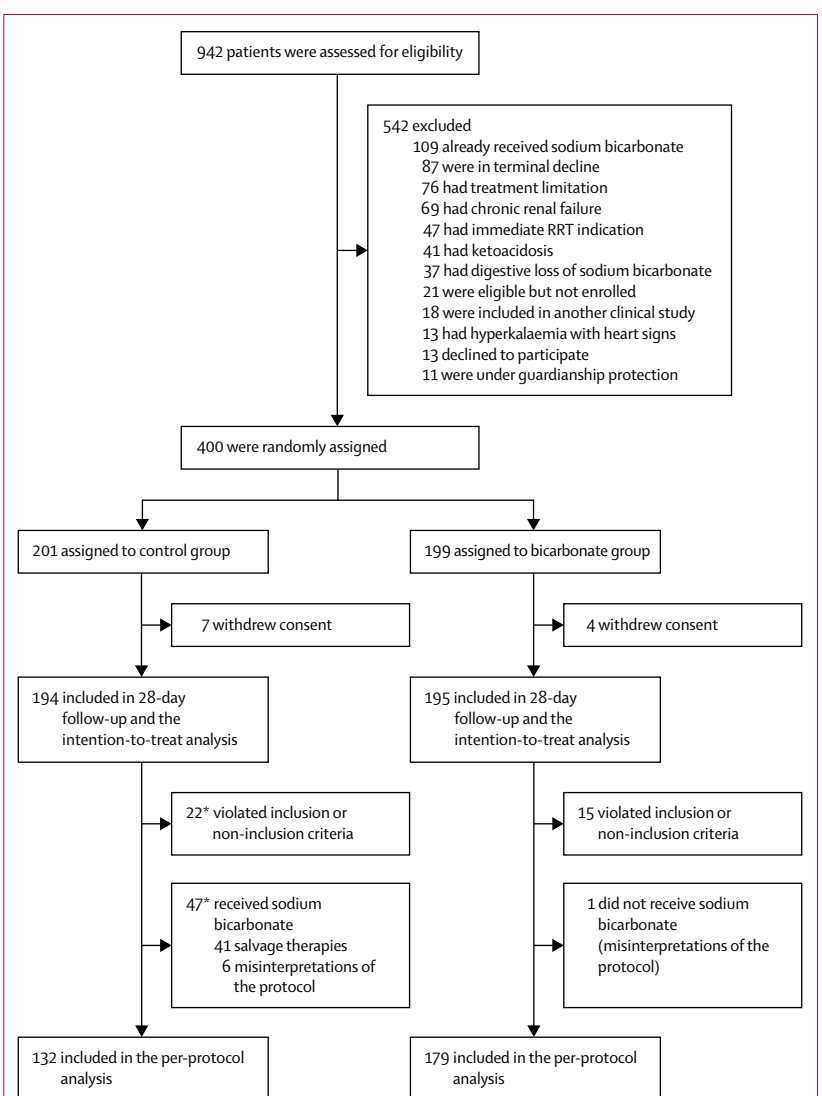
942 patients were assessed for eligibility
542 excluded
109 already received sodium bicarbonate
87 were in terminal decline
76 had treatment limitation
69 had chronic renal failure
47 had immediate RRT indication
41 had ketoacidosis
37 had digestive loss of sodium bicarbonate
21 were eligible but not enrolled
18 were included in another clinical study
13 had hyperkalaemia with heart signs
13 declined to participate
11 were under guardianship protection
400 were randomly assigned
201 assigned to control group
199 assigned to bicarbonate group
7 withdrew consent
4 withdrew consent
194 included in 28-day follow-up and the intention-to-treat analysis
195 included in 28-day follow-up and the intention-to-treat analysis
22* violated inclusion or non-inclusion criteria
15 violated inclusion or non-inclusion criteria
47* received sodium bicarbonate
41 salvage therapies
6 misinterpretations of the protocol
1 did not receive sodium bicarbonate (misinterpretations of the protocol)
132 included in the per-protocol analysis
179 included in the per-protocol analysis

Figure 1: **Trial profile**
RRT=renal-replacement therapy. *Seven patients both violated inclusion or non-inclusion criteria and received sodium bicarbonate.

Demographic characteristics, including Simplified Acute Physiology Score II and McCabe class, were collected at enrolment. Electrolytes were collected for the study's purposes using each site's local laboratory facility at enrolment, 12 h, 24 h, 48 h, and day 7.

	Control group (n=194)	Bicarbonate group (n=195)
Age		
Median age (years)	65 (55–75)	66 (55–75)
≥65	100 (52%)	104 (53%)
<65	94 (48%)	104 (47%)
Sex		
Men	123 (63%)	115 (59%)
Women	71 (37%)	80 (41%)
Body-mass index (kg/m²)	27 (23–30)	26 (23–29)
Simplified Acute Physiology Score II*	60 (48–73)	59 (49–73)
Pre-existing conditions†		
Alcohol abuse	46 (24%)	38 (19%)
Current smoker	61 (31%)	53 (27%)
Diabetes mellitus	43 (22%)	54 (28%)
Chronic hypertension	90 (46%)	88 (45%)
Ischaemic heart disease	28 (14%)	31 (16%)
Chronic heart failure	7 (4%)	8 (4%)
Chronic kidney disease	15 (8%)	14 (7%)
Severe liver insufficiency	17 (9%)	11 (6%)
Cirrhosis	29 (15%)	23 (12%)
Chronic respiratory insufficiency	8 (4%)	9 (5%)
Chronic obstructive pulmonary disease	29 (15%)	18 (9%)
Immunocompromised‡	36 (19%)	30 (15%)
McCabe class§		
0	83 (53%)	94 (56%)
1	62 (39%)	50 (30%)
2	13 (8%)	24 (14%)
Sepsis	115 (59%)	123 (63%)
AKIN status¶		
AKIN 0–1	104 (54%)	103 (53%)
AKIN 2–3	90 (46%)	92 (47%)
Source of admission		
Medical	112 (58%)	110 (56%)
Surgical	82 (42%)	85 (44%)
Main condition associated with acidaemia at enrolment		
Cardiac arrest	18 (9%)	18 (9%)
Septic shock	98 (51%)	107 (55%)
Haemorrhagic shock	40 (21%)	45 (23%)
Others	38 (20%)	25 (13%)
SOFA score‖ at enrolment		
Cardiovascular	4 (4–4)	4 (4–4)
Respiratory	2 (1–3)	2 (1–3)
Neurologic	1 (0–4)	0 (0–3)
Renal	2 (1–3)	2 (0–2)
Hepatic	0 (0–2)	1 (0–2)
Haematological	0 (0–1)	0 (0–2)
Total	10 (7–13)	10 (7–13)

(Table 1 continues on next page)

Outcomes

The primary outcome measure was a composite of death from any cause by 28 days after randomisation and the presence of at least one organ failure at 7 days after randomisation. A-priori secondary outcome measures were the use, duration, and number of days alive free of life-support interventions (such as renal-replacement therapy, mechanical ventilation, and vasopressors); the SOFA score at enrolment and at 1 day, 2 days, and 7 days after enrolment; the total fluid intake between enrolment and day 2; the adverse events of electrolytes that occurred during the ICU stay (plasma pH >7·45, kalaemia >5 mmol/L or <3·2 mmol/L; natraemia >145 mmol/L, and ionised calcaemia <0·9 mmol/L); the occurrence of ICU-acquired infections; and the length of stay in the ICU.

Statistical analysis

This trial was planned with an interim analysis after the observation of the primary outcome of 200 patients (appendix). On the basis of a previous study,[5] we calculated that a total of 376 patients would be needed for an 80% statistical power to show an absolute between-group difference of 15% in the primary outcome at a two-sided α level of 0·03 (0·02 for the interim analysis and 0·03 for the final analysis), assuming that the administration of sodium bicarbonate would be associated with a decrease from 45% to 30% in the primary endpoint. Assuming less than 8% non-analysable patients (loss to follow-up or consent withdrawal), we planned to randomly assign 400 patients.

All analyses were done on data from the intention-to-treat population, which included all patients who underwent randomisation. In the per-protocol analysis, we excluded patients with protocol violations (appendix). We made no imputation for missing values. Baseline characteristics in each study group were analysed as frequencies and percentages for categorical variables and as means and SDs or medians and IQRs for continuous variables, as appropriate. We used an unadjusted χ^2 test for the primary outcome analysis and its two components (ie, death from any cause by 28 days and the presence of at least one organ failure at 7 days). We did a multiple logistic regression for the primary outcome. The survival time was described by means of Kaplan-Meier method and compared with a log-rank test. A Cox proportional-hazards model was used to calculate hazard ratios (HRs) for death. For this analysis, data from all patients were censored at the time of death or at day 28. Logistic and Cox regression models were adjusted on relevant baseline covariates. Covariates were defined as binary variables and continuous variables dichotomised according to their median tested in the model, and were selected in a backward selection procedure if p<0·15 in the univariate analysis and then presented as adjusted odds ratios (ORs) or HRs with 95% CIs (appendix pp 28–34). An adjusted χ^2 test was done to compare day 28 mortality proportion in each group. For multiple comparisons in each prespecified stratum,

a Holm-Bonferroni method was done to compute an adjusted p value. A mixed regression model was used to model repeated measures (appendix pp 18–21). Interactions between variables and time were tested. We also did all the analyses described above among prespecified strata of the randomisation. Tests for all outcomes were two-sided.

We did all analyses with SAS (version 9.2) or R (version 3.2.3). An independent data and safety monitoring committee, who were masked to the group allocation, supervised the conduct of the study and reviewed safety data, with interim analyses done after the inclusion of 100 and 200 patients. This trial is registered with ClinicalTrials.gov, number NCT02476253.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. SJ, HB, NM, and BJ had full access to all the data. The corresponding author had final responsibility for the decision to submit for publication.

Results

From May 5, 2015, to May 7, 2017, a total of 942 patients with severe metabolic acidaemia were assessed for trial eligibility (figure 1). Of these patients, 542 were excluded and 400 were randomly assigned to the study groups (201 in the control group and 199 in the bicarbonate group). After secondary exclusion of 11 patients who withdrew consent, a total of 389 patients were included in the intention-to-treat analysis (n=194 in the control group and n=195 in the bicarbonate group). The characteristics of the patients were well balanced between the two groups (table 1; appendix pp 28, 29). At randomisation, sepsis was present in 238 (61%) of 389 patients and acute kidney injury with AKIN scores of 2 or 3 in 182 (47%) patients. Invasive mechanical ventilation was used in 324 (83%) of 389 patients and vasopressors in 310 (80%) patients. Data for the primary outcome were available for all patients.

Overall, 341 (88%) of 389 patients adhered to the planned treatment in their randomisation group. Sodium bicarbonate was infused in 47 (24%) of 194 patients in the control group, starting at a median of 7 h (IQR 3–27) after randomisation, and in 194 (99%) of 195 patients in the bicarbonate group, starting at a median of 0·2 h (0·1–0·4) after randomisation (table 2; appendix p 17). The proportion of patients in whom the targeted pH of 7·30 was reached and maintained for at least 36 h from enrolment to day 2 was 50 (26%) of 194 patients in the control group and 117 (60%) of 195 patients in the bicarbonate group, taking into account patients who died in the first 48 h (p<0·0001; appendix pp 18, 19). Overall, fluid intake from enrolment to day 1 and from day 1 to day 2 was not different between the two groups (table 2; appendix p 30).

Follow-up data were available for all patients for the primary composite outcome (ie, death by day 28 or at least one organ failure at day 7). The primary outcome occurred in 138 (71%) of 194 patients in the control group and 128 (66%) of 195 in the bicarbonate group (absolute difference estimate –5·5%, 95% CI –15·2 to 4·2; p=0·24; table 2) without significant effect of the treatment group (crude OR 0·775, 95% CI 0·505–1·190; p=0·24; appendix pp 33, 34). The Kaplan-Meier method estimate of the probability of survival at day 28 between the control group and bicarbonate group was not significant (46% [95% CI 40–54] *vs* 55% [49–63]; p=0·09; figure 2A). After multivariate analysis, sodium bicarbonate treatment was significantly associated with fewer deaths than no sodium bicarbonate treatment at day 28 (crude HR 0·783, 95% CI 0·0589–1·040; p=0·091; and adjusted HR 0·727, 95% CI 0·540–0·979; p=0·0356; appendix pp 35, 36).

In the a-priori defined stratum of patients enrolled with acute kidney injury with AKIN scores of 2 or 3, the primary outcome occurred in 74 (82%) of 90 patients in the control group and 64 (70%) of 92 patients in the bicarbonate group (absolute difference estimate –12·3%, 95% CI –26·0 to –0·1; p=0·0462; table 2). The Kaplan-Meier method estimate of survival by day 28 between the control group and bicarbonate group was significant (37% [95% CI 28–48] *vs* 54% [45–65]; p=0·0283; figures 2B, 2C). Univariate and multivariate analysis showed that sodium bicarbonate treatment was significantly associated with better outcome than no sodium bicarbonate treatment at day 28 (primary composite

	Control group (n=194)	Bicarbonate group (n=195)
(Continued from previous page)		
Physiological support†		
Invasive mechanical ventilation	160 (82%)	164 (84%)
Vasopressor support	156 (80%)	154 (79%)
Laboratory results		
Arterial pH	7·15 (7·11–7·18)	7·15 (7·09–7·18)
PaO_2-to-FIO_2 ratio (mm Hg)	229 (142–355)	264 (144–403)
$PaCO_2$ (mm Hg)	37 (32–42)	38 (33–42)
Serum bicarbonate (mmol/L)	13 (10–15)	13 (10–15)
Serum lactate (mmol/L)	5·3 (3·4–9·0)	6·3 (3·6–9·7)
Serum lactate ≥2 mmol/L at enrolment	152 (78%)	168 (86%)
Serum creatinine (mg/dL)	1·76 (1·21–2·48)	1·67 (1·11–2·33)
Blood urea nitrogen (mg/dL)	31 (20–48)	28 (20–45)

Data are median (IQR), mean (SD), or n (%). FIO_2=fractional concentration of oxygen in inspired air. AKIN=Acute Kidney Injury Network. SOFA=Sequential Organ Failure Assessment. *The Simplified Acute Physiology Score II[25] is based on 17 variables; score ranges from 0 to 163, with higher scores indicating more severe disease. †Patients could have more than one pre-existing condition or physiological support, respectively. ‡Defined as >1 mg/kg per day prednisone for 30 days or more, HIV infection, biotherapy, or ongoing chemotherapy. §The McCabe score can range from 0 to 3, with higher scores indicating more severe underlying conditions. McCabe scores were available for 158 patients in the control group and for 168 in the bicarbonate group. ¶AKIN[7,26] stages: stage 1 is serum creatinine increase ≥0·3 mg/dL (≥26·5 µmol/L), increase to 1·5–2·0-times from baseline, or urine output <0·5 mL/kg per h for 6 h; stage 2 is serum creatinine increase >2·0–3·0-times from baseline or urine output <0·5 mL/kg per h for 12 h; stage 3 is serum creatinine increase >3·0-times from baseline or serum creatinine ≥4·0 mg/dL (≥354 µmol/L) with an acute increase of at least 0·5 mg/dL (44 µmol/L), the need for renal replacement-therapy, or urine output <0·3 mL/kg per h for 12 h. AKIN zero means no kidney injury. To convert values for creatinine to µmol/L, multiply by 88·4. To convert values for blood urea nitrogen to mmol/L, multiply by 0·357. ||SOFA[27] includes subscores ranging from 0 to 4 for each of six components (cardiovascular, respiratory, neurological, renal, hepatic, and haematological). Aggregated scores range from 0 to 24, with higher scores indicating more severe organ failure. The SOFA scores at days 1 and 2 after enrolment are shown in the appendix (p 24).

Table 1: **Baseline characteristics of the intention-to-treat population**

endpoint crude OR 0·494, 95% CI 0·246–0·995; p=0·0483; and adjusted OR 0·387, 95% CI 0·163–0·918; p=0·0312; and mortality by day 28 crude HR 0·648, 95% CI 0·435–0·966; p=0·0332; and adjusted HR 0·592, 95% CI 0·392–0·895, p=0·0132; appendix pp 37–40).

In the per-protocol analysis, the primary outcome occurred in 88 (67%) of 132 patients in the control group and 117 (65%) of 179 in the bicarbonate group (p=0·81).

100 (52%) of 194 patients in the control group and 68 (35%) of 195 in the bicarbonate group underwent

	Control group (n=194)	Bicarbonate group (n=195)	Absolute difference estimate (95% CI)	p value
Primary outcome				
Overall population (n=389)				
Composite outcome	138 (71%)	128 (66%)	−5·5 (−15·2 to 4·2)	0·24
Day 28 mortality	104 (54%)	87 (45%)	−9·0 (−19·4 to 1·4)	0·07
At least one organ failure at day 7	134 (69%)	121 (62%)	−2·8 (−15·4 to 9·8)	0·15
Patients with AKIN scores of 2–3* (n=182)				
Composite outcome	74/90 (82%)	64/92 (70%)	−12·3 (−26·0 to −0·1)	0·0462
Day 28 mortality	57/90 (63%)	42/92 (46%)	−17·7 (−33·0 to −2·3)	0·0166
At least one organ failure at day 7	74/90 (82%)	61/92 (66%)	−15·9 (−28·4 to −3·4)	0·0142
Secondary outcomes				
Renal replacement therapy				
Overall population (n=389)				
Use of renal replacement therapy during ICU stay	100 (52%)	68 (35%)	−16·7 (−26·4 to −7·0)	0·0009
Time from enrolment to initiation of renal replacement therapy (h)	7 (3–18)	19 (7–82)	8·8 (3·9 to 15·6)	<0·0001
Renal replacement therapy-free days during ICU stay	8 (0–28)	19 (1–28)	0 (0·0 to 1·0)	0·015
Renal replacement therapy-free days during ICU stay in survivors	28 (25–28)	28 (25–28)	0 (0 to 0)	0·47
Dependence on dialysis at ICU discharge	11/32 (34%)	7/32 (22%)	−12·5 (−34·3 to 9·3)	0·26
Patients with AKIN scores of 2–3* (n=182)				
Use of renal replacement therapy during ICU stay	66/90 (73%)	47/92 (51%)	−22·2 (−36·0 to −8·5)	0·0020
Time from enrolment to initiation of renal replacement therapy (h)	7 (3–17)	20 (8–82)	10·5 (4·0 to 18·5)	<0·0001
Renal replacement therapy-free days during ICU stay	1 (0–22)	10 (1–28)	1·0 (0·0 to 5·0)	0·0040
Renal replacement therapy-free days during ICU stay in survivors	24 (22–28)	28 (19–28)	1·0 (0·0 to 3·0)	0·45
Dependence on dialysis at ICU discharge	10/21 (48%)	5/25 (20%)	−27·6 (−54·1 to −1·1)	0·0465
Other secondary outcomes				
Overall population (n=389)				
Cumulative fluid intake from enrolment to 24 h (mL)	3500 (1500–5250)	3350 (1800–5250)	34·0 (−450 to 500)	0·835
Cumulative sodium bicarbonate volume intake from enrolment to 24 h (mL)	0 (0–0)	500 (250–750)	500 (375 to 500)	<0·0001
Cumulative sodium bicarbonate intake from enrolment to 24 h (mmol)	0 (0–0)	250 (1255–375)	250 (187 to 250)	<0·0001
Cumulative fluid intake from 24 h to 48 h (mL)	1050 (0–2000)	1000 (0–2250)	0 (0 to 250)	0·53
Cumulative sodium bicarbonate volume intake from 24 h to 48 h (mL)	0 (0–0)	0 (0–0)	0 (0 to 0)	0·57
Cumulative sodium bicarbonate intake from 24 h to 48 h (mmol)	0 (0–0)	0 (0–0)	0 (0 to 0)	0·57
Duration of invasive mechanical ventilation (days)	3 (2–8)	3 (2–10)	0·0 (0·0 to 1·0)	0·17
Invasive mechanical ventilation-free days	0 (0–24)	4 (0–24)	0 (0 to 0)	0·48
In survivors	24 (17–26)	23 (14–26)	−1·0 (−2·0 to 0·0)	0·13
Duration of vasopressor therapy (days)	2 (1–3)	2 (1–4)	0 (0 to 0)	0·36
Vasopressor-free days	9 (0–26)	19 (0–26)	0·0 (0·0 to 1·0)	0·10
In survivors	26 (24–27)	26 (23–27)	0·0 (−1·0 to 0·0)	0·34
ICU-acquired infections				
Overall	43 (22%)	48 (25%)	2·4 (−6·1 to 10·8)	0·58
Pneumonia	23 (12%)	29 (15%)	3·0 (−3·8 to 9·8)	0·39
Urinary	10 (5%)	3 (2%)	−3·7 (−7·3 to −0·1)	0·0461
Catheter	6 (3%)	8 (4%)	1·0 (−2·8 to 4·7)	0·61
Unexplained bloodstream infection	14 (7%)	13 (7%)	−0·6 (−5·7 to 4·5)	0·81
Length of ICU stay (days)	4 (1–13)	5 (2–16)	1·0 (−2·7 to 0·0)	0·10
ICU-free days	0 (0–18)	0 (0–18)	0·0 (−1·1 to 0·0)	0·77
In survivors	20 (8–24)	16 (1–24)	−1·0 (−4·0 to 0·0)	0·12

(Table 2 continues on next page)

	Control group (n=194)	Bicarbonate group (n=195)	Absolute difference estimate (95% CI)	p value
(Continued from previous page)				
Patients with AKIN scores of 2–3* (n=182)				
Cumulative fluid intake from enrolment to 24 h (mL)	3150 (1450–5250)	3400 (1500–5500)	150 (–560 to 880)	0·67
Cumulative sodium bicarbonate volume intake from enrolment to 24 h (mL)	0 (0–250)	500 (300–1000)	500 (375 to 500)	<0·0001
Cumulative sodium bicarbonate intake from enrolment to 24 h (mmol)	0 (0–125)	250 (150–500)	250 (187–250)	<0·0001
Cumulative fluid intake from 24 h to 48 h (mL)	600 (0–2000)	1000 (0–2200)	0 (0 to 500)	0·29
Cumulative sodium bicarbonate volume intake from 24 h to 48 h (mL)	0 (0–0)	0 (0–0)	0 (0 to 0)	0·99
Cumulative sodium bicarbonate intake from 24 h to 48 h (mmol)	0 (0–0)	0 (0–0)	0 (0–0)	0·99
Duration of invasive mechanical ventilation (days)	3 (2–8)	4 (2–10)	1·0 (0·0 to 2·0)	0·20
Invasive mechanical ventilation-free days	0 (0–18)	2 (0–21)	0 (0 to 0)	0·13
In survivors	22 (18–28)	20 (12–25)	–2 (–5·0 to 1·0)	0·18
Duration of vasopressor therapy (days)	2 (1–3)	2 (1–4)	0·0 (0·0 to 1·0)	0·46
Vasopressor-free days	1 (0–24)	18 (0–26)	1·0 (0 to 4)	0·022
In survivors	25 (24–27)	25 (22–27)	–0·5 (–2 to 1)	0·73
ICU-acquired infections			..	..
Overall	18/90 (20%)	19/92 (21%)	0·9 (–10·9 to 12·6)	0·88
Pneumonia	13/90 (14%)	14/92 (15%)	0·9 (–9·4 to 11·3)	0·86
Urinary	4/90 (4%)	1/92 (1%)	–3·4 (–8·1 to 1·4)	0·21
Catheter	3/90 (3%)	3/92 (3%)	0·0 (–5·3 to 5·2)	1·00
Unexplained bloodstream infection	9/90 (10%)	3/92 (3%)	–6·7 (–13·9 to 0·5)	0·07
Length of ICU stay (days)	4 (1–11)	7 (1–18)	1·0 (0·0 to 4·0)	0·06
ICU-free days	0 (0–13)	0 (0–14)	0 (0 to 0)	0·40
In survivors	17 (12–22)	13 (0–19)	–3·0 (–8·0 to 0·0)	0·10

Data are n (%), n/N (%), or median (IQR). AKIN=Acute Kidney Injury Network. ICU=intensive care unit. *AKIN[7,26] stages: stage 1 is serum creatinine increase ≥0·3 mg/dL (≥26·5 µmol/L), increase to 1·5–2·0-times from baseline, or urine output <0·5 mL/kg per h for 6 h; stage 2 is serum creatinine increase >2·0–3·0-times from baseline or urine output <0·5 mL/kg per h for 12 h; stage 3 is serum creatinine increase >3·0-times from baseline or serum creatinine ≥4·0 mg/dL (≥354 µmol/L) with an acute increase of at least 0·5 mg/dL (44 µmol/L), the need for renal replacement-therapy, or urine output <0·3 mL/kg per h for 12 h. AKIN zero means no kidney injury. To convert values for creatinine to µmol/L, multiply by 88·4. To convert values for blood urea nitrogen to mmol/L, multiply by 0·357.

Table 2: **Primary and secondary outcomes of the intention-to-treat population**

renal-replacement therapy during their ICU stay (absolute difference estimate –16·7 days, 95% CI –26·4 to –7·0; p=0·0009; figure 3); and when indicated, renal-replacement therapy was started earlier in the control group than in the bicarbonate group (table 2). The number of days alive free from renal-replacement therapy was also significantly lower in the control group than in the bicarbonate group (table 2). Hyperkalaemia and acidaemia were the main reasons for initiation of renal-replacement therapy in the control group (appendix p 41). Sodium bicarbonate treatment was associated with less hyperkalaemia (appendix p 23) and less persistent acidaemia (appendix p 18) than no sodium bicarbonate treatment at day 7. Serum creatinine and serum blood urea nitrogen were the main reasons to start renal-replacement therapy in the bicarbonate group (appendix p 41).

The findings were similar between the overall population and the AKIN 2–3 stratum, with more patients dependent on dialysis at ICU discharge in the control group than in the bicarbonate group (table 2). The number of days free from mechanical ventilation was not different between the two groups for both the overall population and the AKIN 2–3 stratum; and in the AKIN 2–3 stratum, the number of days free from vasopressor was higher in the bicarbonate group than in the control group (table 2). Length of ICU stay did not differ significantly between the treatment groups for the overall population (table 2); length of hospital stay was 12 days (IQR 1–28) in the control group and 15 days (2–28) in the bicarbonate group.

Metabolic alkalosis, hypernatraemia, and hypocalcaemia were observed more frequently in the bicarbonate group than in the control group, with no life-threatening complications reported (appendix p 31). The appendix (pp 31, 32) provides the full details of the metabolic adverse events observed.

Discussion

In this multicentre randomised trial involving critically ill patients with severe metabolic acidaemia (pH ≤7·20), the infusion of sodium bicarbonate, compared with no infusion, to reach and maintain a targeted pH of 7·30 did not significantly decrease the primary composite outcome of mortality by day 28 or the presence of at least one organ failure at day 7 in the overall population. However, sodium bicarbonate infusion decreased the need for renal-replacement therapy during the ICU stay. Moreover, in the a-priori stratum of patients with acute kidney injury at enrolment, infusion of sodium bicarbonate resulted in fewer deaths by day 28 than no infusion of sodium bicarbonate.

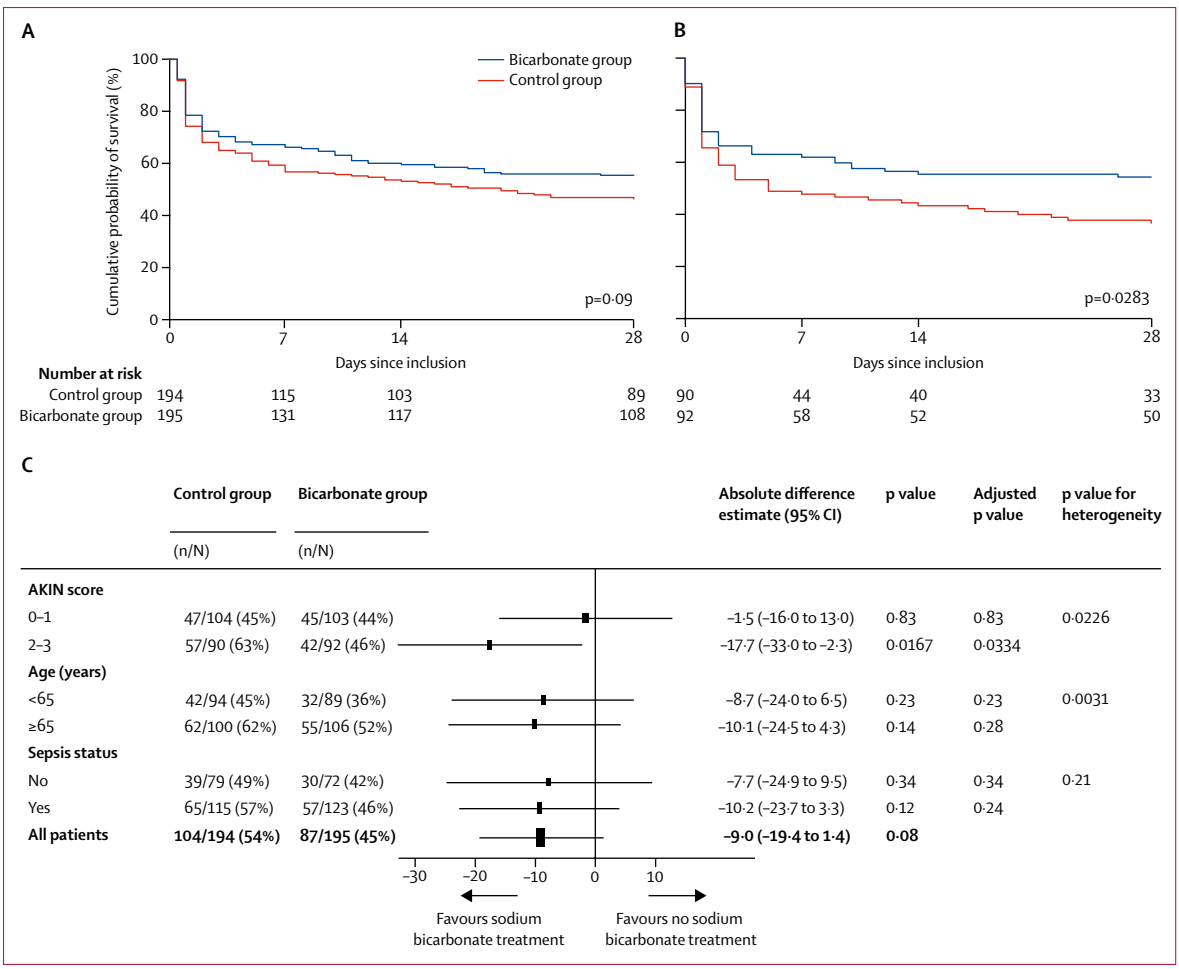

Figure 2: **Time to death in the overall population (A) and patients with prespecified acute kidney injury (B), and the 28-day mortality risk difference in the overall population and in the three prespecified strata (C)**

AKIN=Acute Kidney Injury Network. *A χ^2 test was done to compare day 28 mortality proportion in each group. For multiple comparisons in each prespecified stratum, a Holm-Bonferroni method was done to compute an adjusted p value.

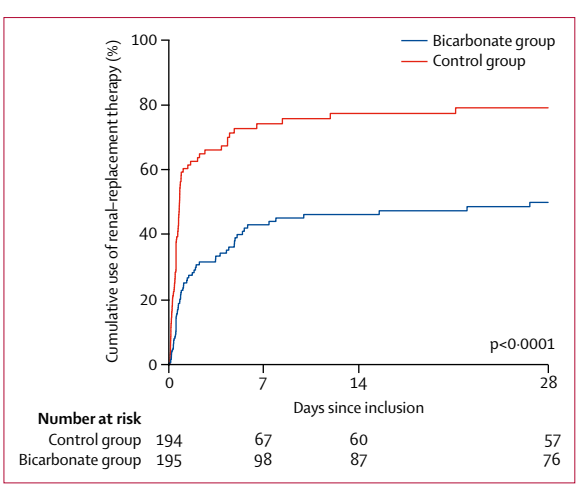

Figure 3: **Cumulative use of renal-replacement therapy from enrolment to day 28 in in the overall population**

The lower mortality in the bicarbonate group among patients with acute kidney injury might have resulted from the combination of more vasopressor-free days and more renal-replacement therapy-free days than for patients in the control group. Sodium bicarbonate infusion in patients with severe metabolic acidaemia and acute kidney injury remains controversial,[9] and a recent meta-analysis[28] from the Cochrane group concluded that there is an inadequate number of randomised clinical trials that have assessed this question. In our trial, almost none of the patients were given sodium bicarbonate in the 24–48 h period, either because of recovery from severe acidaemia or because of death. Although the study was not designed specifically to assess the sodium bicarbonate timing issue, we hypothesise that early sodium bicarbonate infusion is of importance as illustrated by the rapid recovery from severe acidaemia in survivors in our previous observational study,[5] which evaluated severe acidaemia (pH ≤7·20) in the critically ill and its management.

In the AKIKI trial,[29] Gaudry and colleagues showed that a delayed renal-replacement therapy strategy was not associated with a significant difference in mortality in critically ill patients with severe acute kidney injury. In our trial, early sodium bicarbonate infusion might have bought time in patients with unstable severe metabolic acidaemia and either avoided or delayed the initiation of the therapy in some patients. Vasopressor-free days were shorter in the control group than in the bicarbonate group of the AKIN 2–3 stratum. Sodium bicarbonate might also have counterbalanced the deleterious consequences of severe acidosis on myocardial contractility, systemic vasodilatation, tissue perfusion, or cellular function[3,14] that might be associated with vasopressor dependency. Although it could be speculated that delayed or absence of renal-replacement therapy in the control group was associated with more cardiovascular instability, recent trials comparing early versus late renal-replacement therapy in critically ill patients do not support this hypothesis.[29,30] Sodium bicarbonate infusion was associated with metabolic side-effects such as hypernatraemia, hypocalcaemia, and metabolic alkalosis, but none of these episodes were reported as life-threatening in our trial.

There are, however, limitations in our study. No specific control solution was recommended in the control group because there is no fluid without an effect on the acid–base balance. The fluid therapy from enrolment to day 2 was, however, similar in the two groups. Additionally, the physicians caring for the patients in the ICU could not be masked because regular monitoring of arterial blood gases is part of the routine care in patients with severe metabolic acidaemia with a very high risk of mortality. Furthermore, sodium bicarbonate infusion was titrated to reach and maintain a targeted pH of 7·30. However, the endpoints of mortality by day 28 or the presence of at least one organ failure at day 7 were collected and assessed by study members masked to treatment assignment. Another limitation is that the protocol suggested a range of 4·2% sodium bicarbonate volume (125–250 mL per infusion) in the bicarbonate group rather than using a formula to calculate the base deficit and provide a tailored sodium bicarbonate infusion; therefore, we cannot extrapolate whether different ways of administration would have resulted in other outcomes. We also chose not to stratify patients according to the acidaemia mechanism, because the trial was designed to be a pragmatic study. Additionally, the mechanical ventilation settings were not collected. Finally, the causes of acidaemia were heterogeneous, even if septic and haemorrhagic shock were the most common reasons. However, we carefully avoided inclusion of patients with gastrointestinal loss of base or patients with tubular acidosis for whom the indication of sodium bicarbonate infusion is not controversial.

Despite these limitations, our trial presents several strengths, including the multicentre study design, the pragmatism of its design, the well balanced demographic characteristics, and the intention-to-treat analysis, suggesting that its main result might be generalisable to critically ill patients presenting with severe metabolic acidaemia and at least one organ failure.

In conclusion, in patients with severe metabolic acidaemia, sodium bicarbonate treatment had no effect on the primary composite outcome (ie, mortality by day 28 or the presence of at least one organ failure at day 7), but decreased the need for renal-replacement therapy. Additionally, sodium bicarbonate treatment did decrease mortality in the a-priori defined stratum of patients with acute kidney injury. Whether a different protocol of sodium bicarbonate infusion in terms of tonicity or speed of acidaemia correction could influence the outcome remains to be determined and should be evaluated in future trials.

Contributors

SJ, NM, and BJ designed the study and wrote the report. CP, EF, J-YL, SL, TL, JP, AD, MF, KA, JD, LV, P-SA, AdJ, VB, FB, AR, GC, LM, J-MC, HB, and KK approved the design of the study, coordinated individual sites, participated in the inclusion of study participants, and collected the data. All authors revised the report and read and approved the final version before submission.

Declaration of interests

SJ reports receiving grants from the French Ministry of Health and Société Française d'Anesthésie Réanimation; and personal fees from Draeger, Hamilton, Maquet, and Fisher Paykel Healthcare, outside the submitted work. EF reports receiving personal fees from Baxter, Fresenius, and Drager; and non-financial support from Fisher Paykel Healthcare, outside the submitted work. SL reports receiving personal fees from Vifor Pharma and Masimo, outside the submitted work. TL reports receiving personal fees from Baxter, Fresenius, and Merck Sharp & Dohme, outside the submitted work. JP reports receiving personal fees from Medtronic, Getinge, Baxter, and LFB; and non-financial support from Pfizer, outside the submitted work. AD reports receiving grants from the French Ministry of Health and Medtronic; personal fees and non-financial support from Philips, Resmed, and Fisher Paykel Healthcare; and personal fees from Hamilton and Baxter, outside the submitted work. KA reports receiving personal fees from Baxter, Fresenius, Medtronic, LFB, and Merck Sharp & Dohme, outside the submitted work. AR reports receiving personal fees from Merck Sharp & Dohme, outside the submitted work. All other authors declare no competing interests.

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